RESEARCH LETTER

Sensory sensitivity in post–SARS-CoV-2 women

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Introduction The pandemic of COVID-19, a disease caused by SARS-CoV-2, has become a global health crisis.[1] As symptoms resulting from neurologic changes have been reported in COVID-19 patients, the influence of SARS-CoV-2 on the nervous system is being increasingly studied.[2-4] It has been found that coronaviruses can enter the central nervous system (CNS) via transneuronal as well as hematopoietic routes.[2-4]

The most commonly reported CNS-related symptoms of COVID-19 include headaches and / or dizziness, confusion, ataxia, convulsions and, among those related to the peripheral nervous system (PNS), impairment of smell (anosmia) and taste (ageusia).[5-7] Liguori et al[8] demonstrated that in more than 90% of patients with COVID-19, at least 1 neurologic symptom was recorded. In a study by Mao et al,[2] 36.4% of patients with COVID-19 had neurologic symptoms that involved both the CNS and the PNS. Patients who had been hospitalized for COVID-19 described subjective neurologic symptoms, such as fatigue, impaired sleep and wakefulness, headaches and dizziness, muscle pain, paresthesia, as well as anosmia and ageusia, as early indicators of SARS-CoV-2 infection.[9,10]

In studies by Aghagoli et al[6] and Meng et al,[9] it was noted that women are more likely than men to report subjective neurologic symptoms after SARS-CoV-2 infection, in particular abnormal taste or smell, headaches and / or dizziness, numbness / paresthesia, daytime sleepiness, and muscle pain.

To the best of our knowledge, there are no available studies analyzing changes in sensory sensitivity associated with SARS-CoV-2 infection or describing the sensory threshold of COVID-19 survivors in relation to possible cutaneous hypersensitivity associated with this disease. Therefore, the aim of this study was to objectively assess, using transcutaneous electrical nerve stimulation (TENS), the sensory sensitivity of female COVID-19 survivors in relation to factors such as the number of COVID-19 symptoms, time since the disease onset, number of vaccination doses received, and persistent symptoms of so-called long-COVID.

Patients and methods The study involved 151 women with a history of COVID-19. The mean (SD) age of the patients was 43.11 (14.36) years. The participants had a mean (SD) body weight of 70.72 (7.6) kg, height of 167.4 (3.82) cm, and body mass index (BMI) of 25.22 (2.53) kg/m^2.

The study was conducted in a group of women receiving post–COVID-19 physiotherapy treatment at an outpatient clinic. Their main complaints included shortness of breath, impaired exercise tolerance, excessive fatigue during physical activity, and weakness during routine daily activities, none of which had been present before the disease. The study was carried out at the Gierach – MExD Cardiometabolic Centre. All patients gave their verbal consent to participate in the study.

Noninvasive TENS using a biphasic current waveform, with frequency set to 100 Hz and pulse width of 100 μs, was utilized to assess the superficial sensory threshold in the participants. In each patient, the test was performed on the right upper limb, on the group of wrist flexor muscles, to ensure reliability of the results (skin thickness and density of sensory receptors at this site are similar across the female population). To evaluate the sensory threshold, the Aβ sensory fibers were stimulated with current intensity sufficient to evoke a minimal conscious sensation of the stimulus, but not so high as to reach the threshold for movement in the wrist flexor muscles. The intensity of the applied current, expressed in milliamperes (mA), was increased in 0.1-mA increments until a participant reported a minimal, consciously felt tingling sensation.

Ethics This study was conducted in accordance with the Declaration of Helsinki, and approved by the Bioethical Committee of Andrzej Frycz Modrzewski Krakow University (KBKA/4/O/2022).

Statistical analysis Statistical analysis was performed using SPSS 28 software (IBM Corp. Armonk, New York, United States). Normality of the data distribution was checked with the Shapiro–Wilk test. None of the parameters

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Received: February 7, 2024.
Revision accepted: March 22, 2024.
Published online: March 28, 2024.
Pol Arch Intern Med. 2024; 134 (4): 16714
doi:10.20452/pamw.16714

TABLE 1 Correlations between patient characteristics and the level of perceived current intensity expressed in mA

Parameter		Sensory threshold, mA, median (IQR)		
Time since the onset of COVID-19	2–7 weeks	7.85 (7.4–8.7)		
	2–3 months	9.10 (8.2–9.75)		
	3–4 months	9.9 (9.3–10.6)		
	5–6 months	10.7 (10–11.1)		
	7–8 months	10.7 10–11.95)		
	9–10 months	11.1 (10.6–12.4)		
	11–12 months	11.05 (10.2–11.4)		
	>1 year	11.6 (10.5–12.7)		
Number of COVID-19 symptoms	1–4	10.65 (9.9–11.2)		
	5–8	9.55 (8.2–10.6)		
	9–12	9.2 (8.1–10.2)		
Number of COVID-19 vaccination doses	3	10.1 (8.95–11.1)		
	2	11.1 (9.75–11.3)		
	1	11 (10.6–11.2)		
	Unvaccinated	9.15 (8.19.73)		
Parameter		**Spearman rank correlation with the level of current intensity expressed in mA**		
		ρ	**P value**	
Age, y		0.03	0.71	
Weight, kg		0.31	<0.001	
Height, cm		–0.07	0.37	
Number of vaccination doses		0.18	0.03	
Time since the onset of COVID-19		0.75	<0.001	
Number of symptoms		–0.35	<0.001	
Number of long-COVID symptoms		–0.41	<0.001	
Parameter		**Mann–Whitney test**		
		Sensory threshold, mA, median (IQR)	**U**	**P value**
Vaccination status	Unvaccinated	9.15 (8.1–9.73)	1085	<0.001
	Vaccinated	10.3 (9.25–11.15)		
Type of vaccination	Other	11 (9.95–11.25)	377	0.27
	Pfizer	10.2 (9.2–11.18)		
COVID-19 before/after vaccination	Before	11.2 (10.2–11.4)	236.5	0.09
	After	10.25 (9.15–11.1)		
Joint and muscle pain	Absent	10.1 (9.2–11.1)	673	0.006
	Present	8.5 (7.45–10.35)		
Headaches	Absent	10.1 (8.9–11.1)	288	0.42
	Present	9.2 (8.35–11.2)		
Difficulty concentrating	Absent	10.2 (9.25–11.1)	521	<0.001
	Present	8.55 (7.7–9.23)		
Lack of appetite	Absent	10.1 (8.9–11.1)	190	0.23
	Present	8.7 (7.6–10.63)		
Dizziness	Absent	10.1 (8.95–11.1)	535	0.2
	Present	9.15 (8.43–10.45)		
Problems with sleeping	Absent	10.1 (9.2–11.1)	760	0.003
	Present	8.45 (7.7–10.15)		
Weakness and fatigue	Absent	10.4 (9.7–11.2)	991	<0.001
	Present	8.45 (7.7–10.03)		

Abbreviations: IQR, interquartile range

followed a normal distribution; therefore, nonparametric tests (Spearman correlations) were used to analyze relationships between continuous variables. In the case of binary variables, the Mann–Whitney test was used for intergroup comparisons. Qualitative variables were presented as numbers and percentages, and quantitative variables were presented as medians and interquartile ranges. *P* values below 0.05 were considered significant.

Results Most of the women participating in the study (77.49%) were vaccinated against COVID-19; the majority of them (61.59%) received 3 doses of a vaccine, 11.26% received 2 doses, and only 4.64% received a single dose. With respect to the vaccine type, 71.52% of the women were administered the Pfizer / BioNTech vaccine, 3.32% received the AstraZeneca vaccine, and 2.65% were immunized using the Johnson&Johnson vaccine. Most of the women (72.85%) contracted COVID-19 after being vaccinated. A vast majority of the participants (97.35%) were treated at home.

Time interval between the onset of COVID-19 and sensory threshold assessment varied for each participant. In most women (19.21%), the disease occurred 2 to 3 months prior to the examination; 17.22% were sick 2 to 7 weeks before the assessment; 16.56%, 7 to 8 months before; 15.23%, 5 to 6 months before; 10.6%, 11 to 12 months before; 9.93%, 3 to 4 months or 9 to 10 months before; while 1.32% had COVID-19 more than a year prior to enrollment. In the statistical analysis, time between the onset of COVID-19 and participation in the present study correlated positively with the current intensity values expressed in mA recorded during sensory threshold testing ($P < 0.001$) (TABLE 1).

A positive correlation was also found between body weight and the threshold of current sensation ($P < 0.001$) (TABLE 1). In addition, a greater number of COVID-19 symptoms reported by the participants (including, but not limited to fever, dyspnea, cough, rhinitis, headache, fatigue, loss of smell and taste, conjunctivitis) was found to be associated with lower sensory threshold expressed in mA ($P < 0.001$) (TABLE 1).

With regard to vaccination, a greater number of vaccination doses was associated with higher current intensity values needed to reach the sensory threshold ($P = 0.03$).

Persistent post–COVID-19 symptoms (long-COVID) were reported by 31.13% of the women. The patients with joint and muscle pain ($P = 0.006$), difficulty concentrating ($P < 0.001$), problems with sleeping ($P = 0.003$), and those experiencing weakness and fatigue ($P < 0.001$) required lower levels of current intensity to reach the sensory threshold than the women without these symptoms. In addition, as in the case of general COVID-19 symptoms, an increase in the number of long-COVID symptoms was associated with a decrease in the sensory threshold values (P <0.001). Finally, the vaccinated patients required lower current intensity values to reach the sensory threshold than the unvaccinated ones (P <0.001).

Discussion In the various studies available, the prevalence of diseases affecting the PNS in patients with COVID-19 is rather variable, ranging from 1.3% to 9.5% of cases with neuropathy or myopathy,[10,11] up to 70.2%, when taking into account individual symptoms, such as muscle pain or paresthesia.[12]

There are no studies in the literature that objectively assess sensory sensitivity (cutaneous hyperesthesia) in post–COVID-19 patients. The results of our study should therefore be considered preliminary, and constitute an indication for further research, as they cannot be interpreted in the context of similar studies by other authors.

We showed that as the number of COVID-19 symptoms reported by the women increased, the values on the intensity scale during TENS decreased significantly. This means that the sensory sensitivity of the women who reported more COVID-19 symptoms was higher than of those who reported fewer symptoms. Next, a positive correlation was found between the time that had elapsed since the onset of COVID-19 and the sensory sensitivity expressed by the current values needed to reach the sensory threshold. For example, in the women tested more than a year after the onset of COVID-19, current intensity values required to reach the sensory threshold were similar to those reported in healthy women, that is, 11.6 mA in our analysis vs 13.77 mA in a study by Saraiva et al.[13] In the women tested shortly after the onset of COVID-19, sensory sensitivity to current stimulation was significantly increased (eg, 7.85 mA in the group tested 2 to 7 weeks after the disease onset). This finding appears to be consistent with literature reports of other PNS-associated COVID-19 symptoms resolving over time, particularly the ones related to a loss of smell and taste.[14]

In our study, higher values of current intensity were needed to reach the sensitivity threshold in the patients with increased body weight. This is discordant with the results of previous studies assessing the sensory threshold in healthy people and those evaluating individual factors influencing the perception of current stimulation, including the amount of body fat. Related literature[15] indicates that when the current encounters resistance in the form of adipose tissue, it "returns" to the place where tissue hydration is greater, that is, the skin. In such a case, the person exposed to stimulation feels increased current flow through the skin, that is, they require lower current intensity to reach the sensory threshold, and their sensory sensitivity is increased. This is not consistent with the results observed in our analysis of post–COVID-19 women, where increased body weight was shown to favor reduced sensory sensitivity. However, our study included only 9 women with grade I obesity, representing 5.96% of the group, and there were no women with grade II or III obesity. A majority of the women with obesity (n = 8; 5.29% of the whole study group) had COVID-19 between 7 and 12 months prior to enrollment in the study; therefore, it appears that a higher sensory threshold in this group, as compared with the remaining participants, may be due to the time lapse between the onset of the disease and the sensitivity analysis, rather than by increased body weight.

We also found a positive correlation between the number of vaccination doses and the sensory threshold. The women who received fewer vaccination doses required lower current levels to reach the sensory threshold, that is, they were more sensitive. Such a correlation was also observed in the unvaccinated women, who were more sensitive to current stimulation than the vaccinated ones. Therefore, it can be hypothetically concluded that vaccination has a certain protective effect on the occurrence of cutaneous hypersensitivity in patients with COVID-19.

Previously, only 2 studies investigated sensory sensitivity in COVID-19. Krajewski et al[16] reported a new, rare clinical manifestation of COVID-19, that is, cutaneous hypersensitivity. However, they collected data from only 9 patients. Most often, cutaneous hyperesthesia appeared 2 to 3 days after the onset of the general symptoms of the disease. Its duration varied considerably between patients, ranging from 1 day to 6 months. Harsh et al[17] described a case of a 69-year-old woman with moderate COVID-19, in whom any form of touch exacerbated significant cutaneous hypersensitivity, particularly in the abdomen and lower extremities. The hypersensitivity resolved spontaneously after 8 days.

The terms long-COVID and postacute sequelae of SARS-CoV-2 infection refer to the presence of a variety of symptoms that persist after recovery from COVID-19. It should be noted, however, that due to a lack of a clear time criterion for defining long-COVID and a lack of defined timeline of the disease progression, there is no strict timeframe for when long-COVID can be diagnosed.[18] Nevertheless, cases of neurologic symptoms occurring several months after resolution of respiratory symptoms have been reported in the literature. Pain (including headache, joint, and muscle pain) and paresthesia are among the most common long-lasting PNS symptoms following COVID-19, and they are reported in up to 30% of patients in various study groups.[19] Another long-lasting COVID-19 symptom, often described together with dizziness, is fatigue, which persists in up to 53% of patients after resolution of other disease symptoms.[20] In our study, there was an inverse correlation between the presence of long-COVID symptoms, as well as the number of such symptoms, and the current perception threshold. This means that the women with long-COVID symptoms had higher sensory sensitivity than those without persistent symptoms of the disease. The potential predictors of a lower current perception threshold were joint and muscle pain, difficulty concentrating, sleep disorders, and weakness and fatigue. It has been hypothesized that the release of proinflammatory cytokines during acute viral infection can cause hypersensitization of peripheral nociceptors, followed by plastic changes and central sensitization during the chronic stage.[12] This may have influenced the increased sensory sensitivity in women with long-COVID symptoms in our study. However, it seems that symptoms such as sleeping problems or fatigue can cause changes in sensory sensitivity even in the absence of COVID-19. Thus, our findings should be interpreted with caution, especially since this is the first study conducted in this research area.

Conclusions We showed that in the women with a greater number of COVID-19 and persistent long-COVID symptoms, the sensory sensitivity was higher. The patients experiencing joint and muscle pain, difficulty concentrating, sleep disorders, and weakness and fatigue had a lower current perception threshold than the individuals without these symptoms. The potential predictors of reduced sensory sensitivity were the number of vaccination doses received and the amount of time that elapsed since the disease. The vaccinated participants required higher values of current intensity to reach the sensitivity threshold than the unvaccinated ones.

ARTICLE INFORMATION

ACKNOWLEDGMENTS None.

FUNDING None.

CONFLICT OF INTEREST None declared.

HOW TO CITE Błażejewski G, Witkoś J. Sensory sensitivity in post–SARS-CoV-2 women. Pol Arch Intern Med. 2024; 134: 16714. doi:10.20452/pamw.16714

REFERENCES

1 Lytras T, Tsiodras S. Lockdowns and the COVID-19 pandemic: what is the endgame? Scand J Public Health. 2021; 49: 37-40.

2 Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020; 77: 683-690.

3 Harapan BN, Yoo HJ. Neurological symptoms, manifestations, and complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19). J Neurol. 2021; 268: 3059-3071.

4 Leonardi M, Padovani A, McArthur JC. Neurological manifestations associated with COVID-19: a review and a call for action. J Neurol. 2020; 267: 1573-1576.

5 Chaudhury SS, Sinha K, Majumder R, et al. COVID-19 and central nervous system interplay: a big picture beyond clinical manifestation. J Biosci. 2021; 46: 47.

6 Aghagoli G, Marin BG, Katchur NJ, et al. Neurological involvement in COVID-19 and potential mechanisms: a review. Neurocrit Care. 2021; 34: 1062-1071.

7 Keyhanian K, Umeton RP, Mohit B, et al. SARS-CoV-2 and nervous system: from pathogenesis to clinical manifestation. J Neuroimmunol. 2020; 350: 577436.

8 Liguori C, Pierantozzi M, Spanetta M, et al. Subjective neurological symptoms frequently occur in patients with SARS-CoV2 infection. Brain Behav Immun. 2020; 88: 11-16.

9 Meng X, Deng Y, Dai Z, Meng Z. COVID-19 and anosmia: a review based on up-to-date knowledge. Am J Otolaryngol. 2020; 41: 102581.

10 Khedr EM, Abo-Elfetoh N, Deaf E, et al. Surveillance study of acute neurological manifestations among 439 Egyptian patients with COVID-19 in Assiut and Aswan university hospitals. Neuroepidemiology. 2021; 55: 109-118.

11 Frontera JA, Sabadia S, Lalchan R, et al. A prospective study of neurologic disorders in hospitalized patients with COVID-19 in New York City. Neurology. 2021; 96: e575-e586.

12 Taga A, Lauria G. COVID-19 and the peripheral nervous system. A 2-year review from the pandemic to the vaccine era. J Peripher Nerv Syst. 2022; 27: 4-30.

13 Saraiva, LH, Viana L, Pereira LC, et al. Sex and age differences in sensory threshold for transcutaneous electrical stimulation. Fisiother Mov. 2022; 35: e35148.

14 Cooper KW, Brann DH, Farruggia MC, et al. COVID-19 and the chemical senses: supporting players take center stage. Neuron. 2020; 107: 219-233.

15 Seno S, Shimazu H, Kogure E, et al. Factors affecting and adjustments for sex differences in current perception threshold with transcutaneous electrical stimulation in healthy subjects. Neuromodulation. 2019; 22: 573-579.

16 Krajewski PK, Szepietowski JC, Maj J. Cutaneous hyperesthesia: a novel manifestation of COVID-19. Brain Behav Immun. 2020; 87: 188.

17 Harsh IA, Atudorei I, Frank K. Is there a link between COVID-19 and cutaneous hyperesthesia? Confirmation of a recent observation. GMS Hyg Infect Control. 2021; 16: Doc01.

18 Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med. 2021; 27: 601-615.

19 Blomberg B, Mohn KG, Brokstad KA, et al. Long COVID in a prospective cohort of home-isolated patients. Nat Med. 2021; 27: 1607-1613.

20 Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. JAMA. 2020; 324: 603-605.